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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/337,746	06/22/1999	GREGORY M. GLENN	PM-254811	9348

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/337,746	Applicant(s) Glenn et al.
	Examiner G.R. Ewoldt	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 4, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-42, 53-63, and 65-70* is/are pending in the application.

4a) Of the above, claim(s) *70* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-42, 53-63, and 65-69* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *16*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The claims under examination in the instant application are drawn to a method for transcutaneous immunization with an antigen derived from a pathogen. New claim 70 is drawn to a formulation for transcutaneous immunization. Accordingly, Claim 70 is withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

2. Claims 1-42, 53-63, and 65-69 are being acted upon.

3. In view of Applicant's amendment and response, filed 6/04/02, the previous rejection of Claim 10 under the second paragraph of 35 U.S.C. § 112, and the provisional double patenting rejection of Claim 64 have been withdrawn.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-42, 53-63, and 65-69 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for,

a method for transcutaneous immunization (TCI) comprising applying a formulation that does not include a heterologous adjuvant to intact skin, said formulation consisting of cholera toxin (CT), LT, or *Pseudomonas exotoxin A* (ETA), to hydrated skin does not reasonably provide enablement for,

A) a method for TCI comprising applying a formulation comprised of an antigen, wherein said formulation does not include a heterologous adjuvant to intact skin,

B) a method for TCI comprising activating at least one antigen presenting cell underlying where the formulation's site of application,

C) a method for TCI comprising an APC wherein the APC is a Langerhans cell,

D)a method for TCI comprising applying an antigen in whole cell form,

E)a method for TCI comprising applying an antigen comprising a viral particle or virion,

F)a method for TCI comprising applying diphtheria toxin (DT),

G)a method for TCI wherein the induced immune response recognizes a lipopolysaccharide (LPS).

H)a method for TCI wherein the induced response recognizes influenza virus hemagglutinin (HA), influenza virus nucleoprotein (NP), Hemophilus influenza B polysaccharide conjugate (Hib-PS), and *Escherichia coli* colonization factor CS6.

I)a method for TCI wherein underlying endosomes or lysosomes are lysed, for the reasons of record as set forth in Paper No. 19, mailed 12/04/01.

Applicant's arguments, filed 6/04/02, have been fully considered but they are not persuasive. Applicant argues that,

"The claimed invention is directed to transcutaneous immunization with antigen which is sufficiently immunogenic that adjuvant is not needed or with a molecule that includes both antigen and adjuvant activities. Molecules which do not require "heterologous adjuvant" include ADP-ribosylating exotoxins, pathogen associated molecular patterns (PAMPs), and cytokines [*sic*] Of course, as taught by the specification and exemplified, there are also antigens that require adjuvant activity to induce an antigen-specific immune response by transcutaneous immunization: diphtheria toxoid (DT), tetanus toxoid (TT), and CS6. Therefore, using the guidance provided in Applicants' specification, it would not require undue experimentation to determine whether an antigen was sufficiently antigenic to not require an adjuvant or a molecule included both antigen and adjuvant activities."

This argument appears to indicate that the guidance of the specification comprises a claim that if an antigen works in the claimed method it is encompassed by the method and if an antigen does not work in the claimed method it is not, i.e., trial and error. It is the Examiner's position that a disclosure providing only a guidance to trial and error provides an insufficient expectation of success, and therefore cannot be considered an enabling.

Applicant argues, "As an initial matter, Applicants note that the objections quoted above are mostly directed to the lack of working examples for limitations recited in dependent claims." The Examiner's position could more accurately be stated as, given the admitted unexpected nature of the invention of the instant claims, some enabling disclosure, particularly in regards to specific limitations, e.g., the mechanisms by which the instant invention functions, would be required. Working examples, while not required, comprise the most effective demonstration of unexpected results. Applicant further argues, "examples have already been disclosed in previously-filed application [*sic*]

which were incorporated by reference in this specification." However, the Examiner has not found examples which demonstrate either the breadth of the claims, e.g., TCI absent adjuvants (or antigens known to possess adjuvant properties) or specific limitations of the claims, e.g., examples which demonstrate the activation of Langerhan's cells. Applicant argues that Examples 17 and 18 support, and are not inconsistent with previous teachings. While Example 17 states that the known adjuvant CT causes an "enhancement" of MHC Class II expression on Langerhan's cells and a change in morphology (no data is disclosed), Example 18 comprises merely a discussion of Langerhan's cell activation/ migration with the disclosure that "We envision that cholera toxin (CT) and its B subunit (CTB) might upregulate the expression of ICAM-1 and downregulate the expression of E-cadherin on Langerhan's cells as well as upregulate the expression of MHC class II molecules on the Langerhans cell." It remains the Examiner's position that said disclosure/discussion/speculation is insufficient enablement given the unexpected and unpredictable nature of the invention of the instant claims.

Applicant argues that "physical or chemical penetration may be used to enhance the induction of an immune response by whole virus or bacterium by exposing the stratum corneum. But even large biomolecules like nucleic acids are able to induce an immune response when applied to skin which has not been pretreated other than by hydration." Regarding the use of additional "physical or chemical penetration" said penetration comprises an unclaimed limitation that is not recited in base Claim 1. Further it remains the Examiner's position that as Applicant has admitted that the invention of the instant claims is based on findings "that would not be expected" based on the prior art (page 5 of the specification), it is Applicant's burden to establish that the invention of the instant claims in enabled in its breadth.

Thus, Applicant's assertion that "The weight of evidence in support of the enabling nature of the disclosure of the specification is firmly in favor of the conclusion that undue experimentation would not be needed to practice the present invention and that the enablement rejections are not supported by any factual evidence," is simply scientifically and legally incorrect. "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in

the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable. Additionally, the MPEP indicates that unpredictability may be established by the fact that claims are drawn to an invention that is "contrary to accepted scientific principles," a situation which in this case Applicant has admitted in the specification. Applicant has demonstrated the highly unexpected findings with only a narrow range of closely related known adjuvants, and has not demonstrated any mechanisms by which the claimed invention (TCI) functions. Thus, claims drawn to specific mechanisms, and broad methods absent any known adjuvant, cannot be considered enabled by the instant specification, given the unexpected nature of the invention of the instant claims.

6. Claim 58 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention, for the reasons of record as set forth in Paper No. 19, mailed 12/04/01.

Applicant's arguments, filed 6/04/02, have been fully considered but they are not persuasive. Applicant argues that "Applicants' specification teaches the physical and chemical composition of such conjugates on page 13, line 8, to page 15, line 8. A variety of known targeting molecules are described to form a conjugate with the antigen." While the cited section may disclose certain targets on antigen presenting cells, there is no disclosure of the claimed "heterologous molecules" which might target the targets. Neither does the cited section at page 19, line 26 - page 21, line 16 disclose sufficient "heterologous molecules" to support the claim.

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805 The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Patrick J. Nolan

G.R. Ewoldt, Ph.D.
Patent Examiner
Technology Center 1600
August 1, 2002

Patrick J. Nolan, Ph.D.
Primary Examiner
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